Female sex hormones and OCP

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Introduction

- Estrogen:-
  - Natural and synthetic

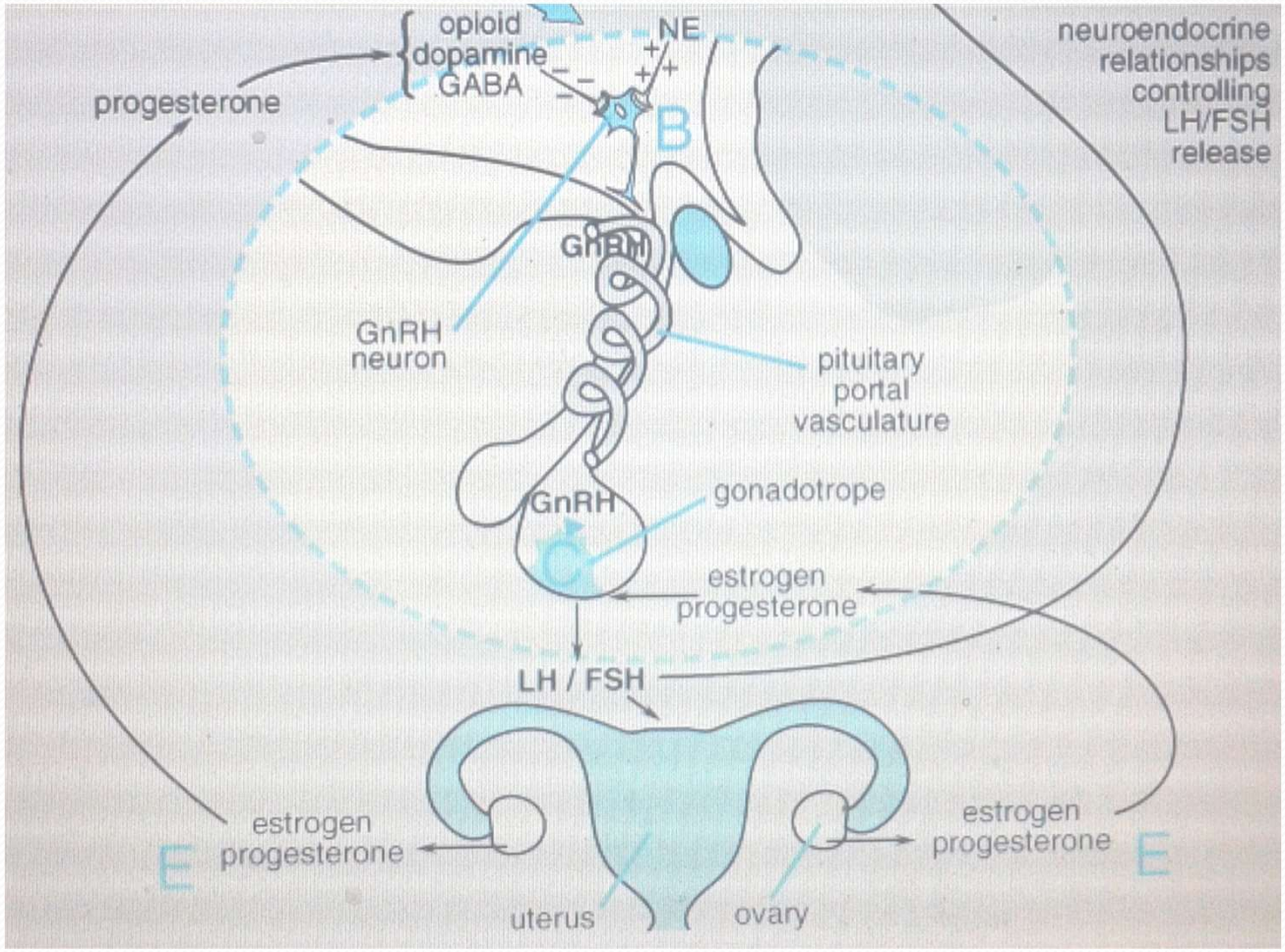
- Natural
  - Estriol, **estradiol** and estrone
  - Synthesized in ovary

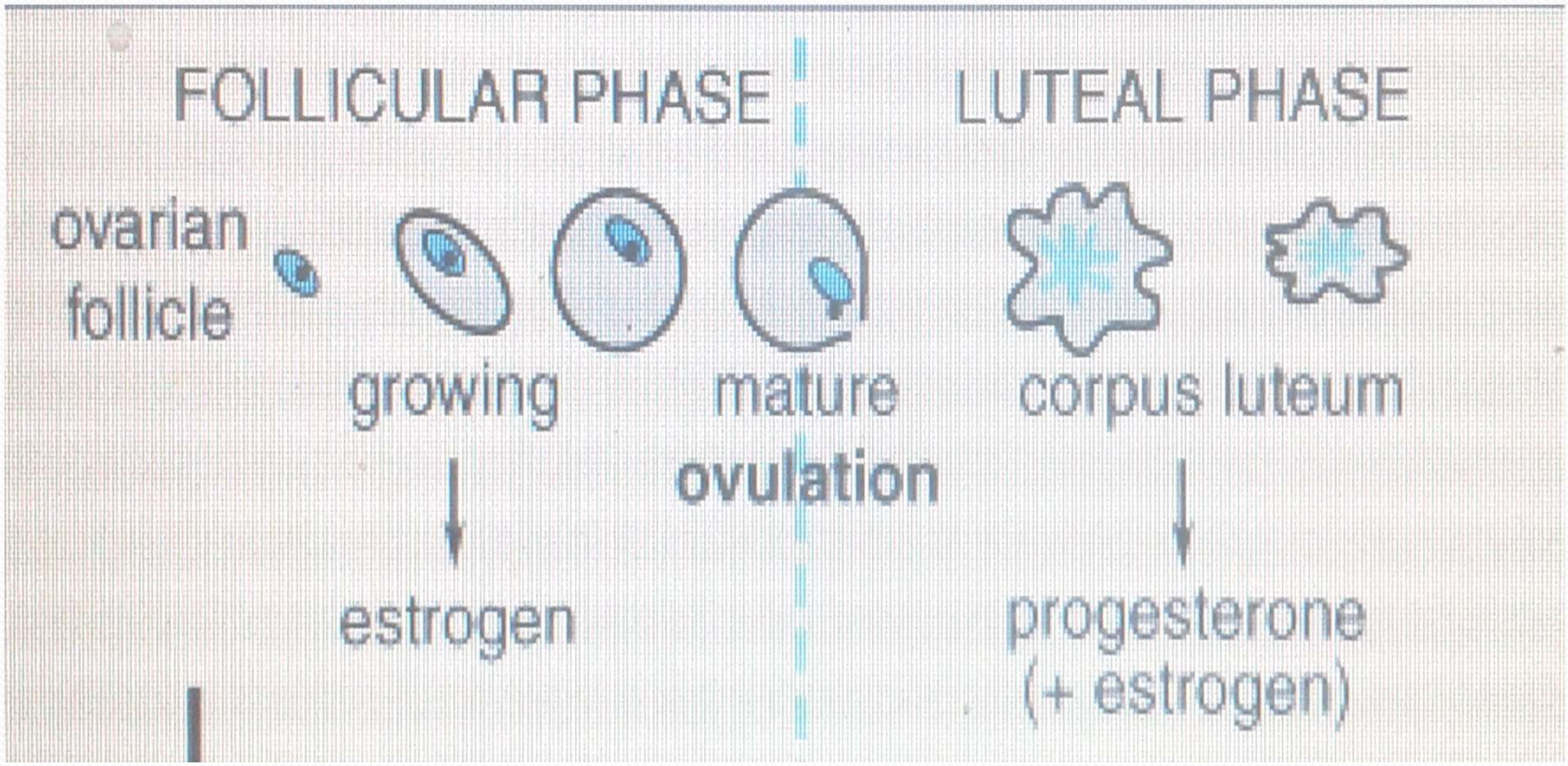
Classification

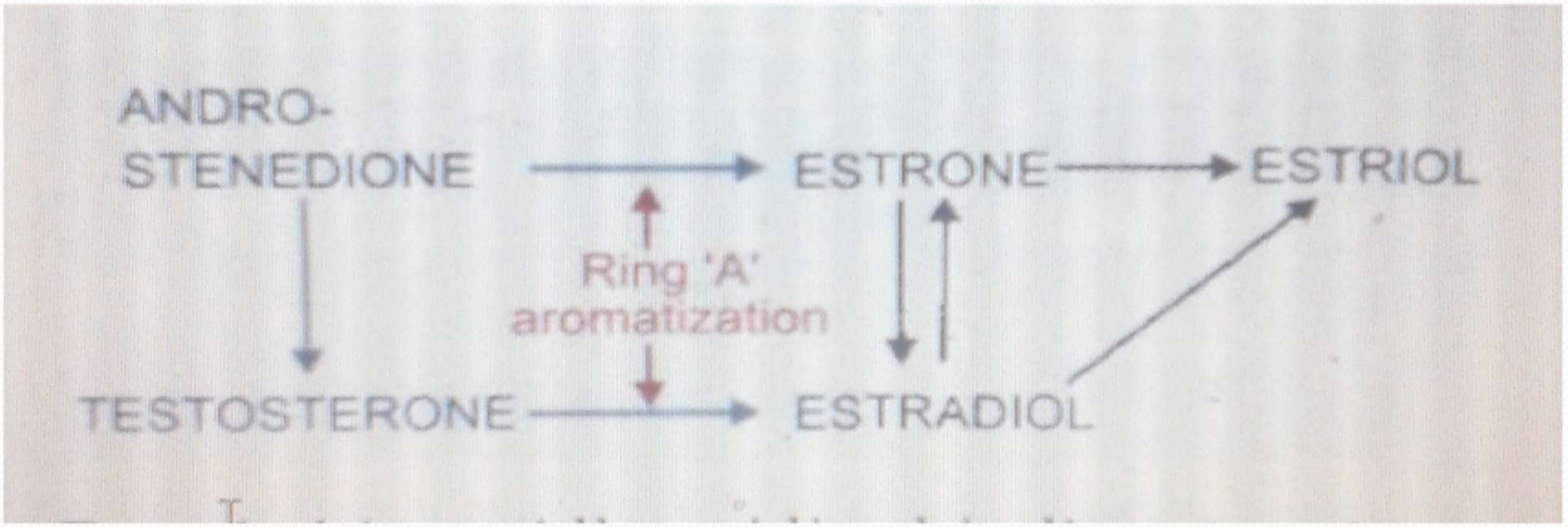
- Synthetic
  - Natural are inactive orally, short acting
  1. Steroidal
     - Ethinylestradiol, mestranol
  2. Non steroidal
     - Diethylstilbestrol

Regulation of secretion

- FSH




FOLLICULAR PHASE
LUTEAL PHASE
ovarian follicle
growing
mature
corpus luteum
ovulation
estrogen
progesterone (+ estrogen)


ANDRO-
STENEDIONE
ESTRONE
ESTRIOL
Ring 'A'
aromatization
TESTOSTERONE
ESTRADIOL

Pharmacological actions

1. Sex organs:-
   - Growth
   - Proliferation phase
2. Secondary sex characters
   - Feminine growth
3. Metabolic
   - Anabolic, Good HDL: LDL ratio, Worsening of diabetes & bone mass (Osteoclast inhibition & activation of Vit D3 in renal system)

Mechanism of action

- Nuclear receptors in target cells (ER)

P/K

- Naturals :- can be given IM
- Synthetic:- more potent, orally active
- Preferred route :- oral
- Transdermal patch:- slightly beneficial than other routes

Preparation

- Both oral and parenteral route efficacies are similar
- Oral route is preferred
- IM injection in case of high dose
- Estradiol- TTS

Adverse effects

- In children:-
  - Reduction of stature
- In male:-
  - Gynecomastia, suppression of libido, feminization
- In female:-
  - Breast cancer, endometrial carcinoma, irregular bleeding,
- In pregnant women:-
  - Vaginal or cervical carcinoma, genital abnormalities
- Long-term theapy:-
  - Gallstones
- Migraine, epilepsy, endometriosis worsened

Therapeutic hormones

1. HRT(Hormone Replacement Therapy)
   - Occurs at menopause
   - Sign/symptoms
     - Vasomotor disturbances (hot flushes, chilly sensation)
     - Vaginal atrophy (vaginitis, itching, UTI)
     - osteoporosis
     - Skin (drying, loss of elasticity)
     - Psychological (irritability, depression)
     - Increased risk of cardiovascular diseases

- Treatment :- Limited use due to toxic side effects on long term use (increase risk of MI, breast cancer due to progestins)
  1. Combined HRT :-
     - estrogen (0.3 mg/day) for 3 weeks along with progestin - norethisterone (2.5 mg/day) for last 10-12 days (reduce DUB)
     - Alone when hysterectomised patient or progestin is not tolerable or contraindicated
     - For menopause, osteoporosis
  - Conditions:
  1. Within 10 years of menopause
  2. Not in age > 60 years
  3. No long term treatment

- Tibolone :-
  - Estrogenic, androgenic and progestational property
  - Lesser side effects
2. Delayed puberty in girls
3. Dysmenorrhoea: Reserved for severe cases
4. DUB:- progestin, estrogen have adjuvant role

SERMs

- Tamoxifen citrate, Raloxifene, Toremifene
- Agonistic and antagoinistic action
- Selective estrogen receptor modulators
- Risk of DVT & pulmonary embolism

Therapeutic uses

1. Anovulatory infertility:-
   - **Clomiphene citrate** (50 mg daily for 5 days starting from 5th day of cycle)
   - Antagonist on all receptors (Antiestrogen)
   - Side effects:- hot flushes, osteoporosis, polycystic ovaries, multiple pregnancies (No more than 6 treatment cycles)
2. Breast cancer:-
   - **Tamoxifen citrate**
   - Antagonist at breast, blood vessels while partial agonist at uterus, bone, liver and pituitary
   - Primary as well as metastatic breast carcinoma in premenopausal women, In postmenopausal, replaced with AI after 2 years

3. Osteoporosis
   - **Raloxifene citrate**
   - Partial agonist at bone, cardiovascular system and antagonist at breast, uterus
   - Risk of vertebral fractures reduced
   - Second line drug for prevention & treatment of osteoporosis
4. Contraceptive
   - **Ormeloxifene**
   - Antagonist in breast and cancer
   - Also used in
5. DUB (dysfunctional uterine bleeding)

Antagonists

- Fulvestrant:-
  - Pure estrogen receptor antagonist or Selective Estrogen Receptor Down Regulator (Inhibits dimerization of Ers)
  - For ER positive breast cancer in postmenopausal women in tamoxifene resistant cases
- Letrozole, anastozole (type 2), exemestane (type 1)
  - Aromatase inhibitors

- Good for postmenopausal women

1. Early breast cancer: tamoxifene is replaced by AI after 2 years of treatment to reduce DVT
2. Advanced breast cancer:
3. Tamoxifene resistant cases

* Not recommended in Premenopausal women

Side effects:

Hot flashes, Vaginal dryness, Nausea, Dyspepsia, diarrheoa

Progestins

- Convert proliferative into secretary phase
- Maintain pregnancy
- Natural and synthetic

Classification

- Natural:-
  - Before pregnancy:- corpus luteum
  - After pregnancy:- placenta

- Synthetic:-
  - Progesterone derivatives:- medroxyprogesterone acetate
  - 19-nortestosterone derivatives:- norethindrone, norethisterone, levonorgestrel
    - Newer:- norgestimate, gestodene, desogestrel

Pharmacological action

1. Uterus:- secretory changes
2. Breast:- during pregnancy, for lactation
3. Metabolism:- reverse HDL:LDL ratio

Mechanism of actions

- Same as estrogen

Pharmacokinetics

- Orally inactive; high first pass metabolism
- IM injections
- Synthetic :- orally active

Adverse effects

- Worsening of HDL:LDL ratio
- Blood sugar rises
- Irregular bleeding
- Congenital deformities

Therapeutic uses

1. Contraception
2. HRT
3. DUB
4. Endometriosis
5. PMS
6. Threatened abortion
7. Endometrial carcinoma

Antiprogestins

- Mifepristone (antiglucocorticoid, antiandrogen)
  - Follicular phase:- delay ovulation
  - Secretory phse:- increase PGs
  - Fertilization phase:- make dislodgement of fetus
- Uses:-
  1. Termination of pregnancy:-
     - Upto 7 weeks:- 600 mg single oral dose
     - First trimester abortion:- f/b 400 mg

2. Cervical ripening:-
   - Induction of labor

3. Post coital contraceptive (72 hours)
   - 600 mg

4. Cushing's syndrome

Hormonal contraceptives

- Reversible suppression of fertility
- Female contraception:- different types

1. Oral:-

a) Combined pills:-

- Etinyl estradiol 30 ug + norgestimate 200 ug
- For 21 days, starting on 5th day of menses
- 7 days for gap period, bleeding occurs
- Most effective (99.9%)

b) Phasic regimens
   - Biphasic or triphasic

c) Minipill:- (progesterone only pill)
   - Less effective (96-98%)

d) Post coital :-
   1. Ethinyl estradiol 50ug+ levonorgesterel 250 ug
   - Two tablets within 72 hours, repeat after 12 hours
   2. Levonorgesterel alone 0.75 mg 12 hourly within 72 hours
   3. Mifepristone 600 mg within 72 hours

2. Injectable:-
    a) DMPA:- 150 mg at 3 months interval IM
    b) NET-en:- 200 mg at 2 months
    c) MPA + estradiol :- once a month
3. Implants:-
    a) Norplant:- set of 6 capsules, each releasing 36 mg levonorgestrel, work for 5 years
4. IUCD:-
    a) Progesterone containing

Mechanism of action

- FSH, LH inhibition….antiovulatory effect
- Cervical mucus, endometrium….unfavorable for implantation

1. Discontinuation:- pregnancy after 1-2 months
2. Two tablets on next day on missing single day
3. If two missed, interrupt course and use other method
4. If occurs during OC pills, terminate by suction
5. Centchroman :- developed by India, SERM
   - 30 mg twice weekly for 3 months f/b once weekly until pregnancy want
   - Reduce tube mortality

- Male contraceptives

1. Complete suppression difficult
2. Drug takes long time for effect

Examples

1. Antiandrogen
2. Estrogen
3. Cytotoxic drugs
4. gossypol

Thank you